The addition of induction chemotherapy with etoposide, ifosfamide, and cisplatin failed to improve therapeutic outcome of concurrent chemoradiotherapy in patients with locally advanced non-small cell lung cancer – single institution retrospective analysis

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Although chemoradiotherapy (CRT) is a standard treatment for unresectable locally advanced non-small cell lung cancer (NSCLC), the optimal sequencing remains to be determined.

We retrospectively compared the treatment results of induction chemotherapy followed by concurrent CRT (induction group, 32 patients) with those of concurrent CRT alone (concurrent group, 41 patients) in unresectable stage IIIA/IIIB NSCLC patients. In induction group, 2 cycles of induction chemotherapy (etoposide/ifosfamide/cisplatin: 24 patients, others: 8 patients) were followed by concurrent CRT (60 Gy/30 fractions, 6 mg/m^2 of cisplatin daily), while the same concurrent CRT was administered in concurrent group.

Clinicopathologic characteristics including age, weight loss, histologic types, and clinical stage did not show significant differences between two groups except for a higher proportion of patients with ECOG performance status 2 in concurrent group (3% vs. 27%, p=0.015). Overall toxicity was generally acceptable with 1 treatment-related death from tracheoesophageal fistula in induction group. The response rates after concurrent CRT were 41% for induction group and 54% for concurrent group, which showed no significant difference (p=0.560). With median follow-up of 13 (1–92) months, there was a trend toward an advantage for concurrent group in median progression-free survival (6 months vs 8.3 months, p=0.067) and overall survival (12 months vs. 14.5 months, p=0.059). In multivariate analysis, only more than 10% weight loss within 6 months was significantly associated with poor survival (p=0.001).

In conclusion, the addition of induction chemotherapy to concurrent CRT did not show any advantage over concurrent CRT alone in locally advanced NSCLC.

Key words: non-small cell lung cancer, locally advanced, induction chemotherapy, concurrent chemoradiotherapy

Lung cancer is the most common malignancy in many countries and it has become the first cause of cancer death in Korea surpassing gastric cancer [1, 2]. Majority of lung cancer patients have non-small cell type and locally advanced unresectable non-small cell lung cancer (NSCLC) represents approximately 35–40% of newly diagnosed cases of NSCLC [2]. Many randomized clinical trials and meta-analysis have demonstrated that combination of chemotherapy and radiotherapy is superior to radiotherapy alone in locally advanced unresectable NSCLC, suggesting chemoradiotherapy (CRT) as a standard treatment for such patients with good prognostic factors [2–7].

The most frequently investigated treatment approach is induction chemotherapy followed by radiotherapy [2]. Survival advantage of induction chemotherapy followed by radiotherapy over radiotherapy alone was demonstrated in Cancer and Leukemia Group B 8433 and Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group (ECOG) 88-08 trials [5, 7, 8]. On the other hand, the European Organization for Research and Treatment of Cancer

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(EORTC) showed that the concurrent administration of low dose cisplatin with radiation improved local control and overall survival compared with radiotherapy alone [4].

Although CRT is established as a standard treatment for locally advanced unresectable NSCLC, the sequencing of radiotherapy and chemotherapy is a major area of controversy [2]. While the beneficial effect of sequential approach is mainly attributable to eradication of systemic metastasis, improved local control resulted in better survival in patients treated with concurrent CRT [2]. Therefore, combining the induction chemotherapy and concurrent CRT is theoretically appealing because it may effectively control the primary lesion while even attempting to eradicate occult distant micrometastasis [2, 9]. Under these backgrounds, we retrospectively compared the results of unresectable stage III NSCLC patients treated with induction chemotherapy followed by concurrent CRT with daily low dose cisplatin with those of patients with concurrent CRT alone.

Patients and methods

Patients. All patients were required to have the followings to be a candidate of CRT; (1) histologically or cytologically documented NSCLC; (2) previously untreated; (3) locally advanced unresectable clinical stage IIIA/IIIB disease according to the American Joint Committee on Cancer [10]; (4) ECOG performance status (PS) 0–2; (5) no other significant medical disease. Patients with pleural effusion were not eligible for CRT, while those with supraclavicular lymph node metastasis were included. Each patient underwent the following staging procedures: chest radiography, chest computed tomography (CT) scan, radionuclide bone scan, imaging of upper abdomen (ultrasound or CT scan), and hematologic and biochemical profiles.

In CRT, two different treatment approaches were applied. Between March 1995 and December 1996, all patients who were candidates for CRT were treated with 60 Gy of thoracic irradiation with 6 mg/m^2 of intravenous cisplatin daily, which is similar to treatment regimen of EORTC [4].

Radiotherapy was administered on linear accelerator (CLINAC 2100C, Varian Medical Systems, Palo Alto, CA, USA). Irradiation was delivered 2 Gy per fraction, 5 days a week, to a total dose of 60 Gy. We used parallel opposing field and the radiation field included a gross tumor volume and margin, which was 2 cm supero-inferiorly, 1 cm laterally. The spinal cord was limited to 40 Gy.

Since January 1997, the patients who fulfilled the above mentioned criteria and with good performance status (ECOG 0, 1) were treated with induction chemotherapy followed by concurrent CRT. Patients who refused this protocol or with ECOG PS 2 were treated with concurrent CRT alone. Induction chemotherapy followed by concurrent CRT consisted of 2 cycles of induction chemotherapy with 3–4 week intervals prior to CRT. The most commonly administered induction chemotherapy regimen was VIP (etoposide 80 mg/m^2, ifosfamide 1.5 g/m^2, cisplatin 20 mg/m^2 on day 1–3; 24 patients), followed by TP (docetaxel 75 mg/m^2 day 1, cisplatin 25 mg/m^2 day 1–3; 6 patients), gemcitabine/cisplatin (1 patient) and etoposide/cisplatin (1 patient). Concurrent CRT started 3–4 weeks after completion of induction chemotherapy and the schedule was same as in concurrent CRT alone group. Radiation technique was identical in the two treatment protocols, although radiation field was assessed based on the radiologic findings after induction chemotherapy in induction chemotherapy followed by CRT group.

In both groups, one or more cycles of maintenance chemotherapy were given to patients after radiotherapy if possible.

Evaluation. Tumor responses to induction chemotherapy and CRT were evaluated with plain chest x-ray just before CRT and chest CT scan 4–6 weeks after completion of CRT, respectively. Then, chest x-ray was performed monthly up to 6 months, every 2–3 months for 2 years, and every 6 months thereafter. More sophisticated diagnostic work-up including chest CT scan was performed only if clinically indicated.

Response to treatment was evaluated according to the World Health Organization criteria [11]. The complete response was defined as the complete disappearance of all symptoms and signs of tumor for more than 4 weeks. The partial response was defined as a reduction by 50% or more of the sum of the products of all measurable lesions lasting more than 4 weeks. Stable disease was indicated by a less than 50% reduction or less than 25% increase in tumor size. Progressive disease was defined as an increase of more than 25% in tumor size or the appearance of new lesions. Toxicity was assessed using the World Health Organization criteria except for radiation pneumonitis and esophagitis, which were evaluated by National Cancer Institute criteria [11, 12].

Statistical analysis. Progression-free survival (PFS) and overall survival (OS) were calculated using KAPLAN-MEIER method [13]. PFS was defined as the time from start of treatment to disease progression, or second primary cancer, or death from any other cause. Data on patients who did not have a progression were censored at the last follow-up. OS was defined as the time from start of treatment to death; data on survivors were censored at the last follow-up. The differences between the survival curves were tested by using the log-rank test. Comparison of clinicopathologic characteristics was evaluated with the Mann-Whitney test and Chi-square test. Cox proportional-hazards regression model was used to determine the joint effects of several variables on survival [14].

Results

Patient characteristics. Between March 1995 and December 2001, 73 patients were treated with either induction chemotherapy followed by concurrent CRT (induction group, 32 patients) or concurrent CRT alone (concurrent group, 41 patients). Since January 1997, when combined induction chemotherapy and CRT protocol was initiated, 9 patients re-

ceived concurrent CRT alone because of ECOG PS2 or patient/physician's choice, while 32 patients were treated with induction protocol. No statistically significant differences were found in pretreatment clinicopathologic characteristics including age, weight loss, histologic types and clinical stage except for a higher proportion of patients with ECOG PS 2 in concurrent group (3% vs. 27%, p=0.015) (Tab. 1).

In induction group, 22 patients (69%) completed treatment as planned. Two patients refused further treatment after induction chemotherapy, and 1 patient underwent palliative radiotherapy because of bone metastasis after 1 cycle of induction chemotherapy. Two patients did not receive daily cisplatin during radiotherapy due to decreased performance status, and 1 patient did not complete CRT as planned. Four patients (13%) finished radiotherapy but did not complete daily cisplatin as planned. In concurrent group, 4 patients did not complete CRT and 8 patients finished radiotherapy without completion of daily cisplatin. Therefore, twenty-nine patients (71%) completed concurrent CRT according to treatment protocol. Nine patients (28%) in induction group and 11 patients (27%) in concurrent group received maintenance chemotherapy after CRT, respectively. In induction group, median cycle of maintenance chemotherapy was 2 (1–6 cycles) and 8 patients received VIP regimen (1 patient: etoposide/cisplatin). In concurrent group, 10 patients received maintenance chemotherapy with etoposide/cisplatin while VIP regimen was administered in 1 patient and median cycle was 4 (1–6 cycles).

Toxicity. Although toxicity of induction chemotherapy was generally acceptable, a quarter of patients experienced grade 3/4 neutropenia or leukopenia (Tab. 2). There was no significant difference in toxicity of CRT between induction and concurrent group, and most toxicity was grade 1 or 2 (Tab. 3). In terms of treatment-related death, 1 patient in induction group died of tracheoesophageal fistula.

Treatment response. After 2 cycles of induction chemotherapy, 5 patients (16%) achieved partial response. Stable disease and progressive disease were observed in 22 (69%) and 5 (16%) patients, respectively. The response after concurrent CRT was 41% for induction group and 53% for concurrent group, which showed no significant difference (p=0.560) (Tab. 4).

Pattern of failure. The patterns of first failure showed no significant difference between two groups. Fifty-six percent of patients in induction group and 44% in concurrent group had progression of disease in primary site and/or thorax, respectively (Tab. 5).

Survival. The median follow-up duration was 13 months (range: 1–92 months) and no patient was lost to follow-up. At the time of analysis, 72 of 73 patients have died and 69 deaths were attributable to progression of lung cancer. One patient died of treatment-related complication, while the causes of death were undetermined in two patients. Median PFS was marginally superior in concurrent group (6 months vs. 8.3 months; p=0.067) (Fig. 1). The 2-year OS rate and median survival time were 19% and 12 months in induction group compared with 37% and 14.5 months in concurrent group, respectively, with a tendency of better survival in concurrent group (p= 0.059) (Fig. 2). In multivariate analysis, only more than 10% weight loss during the 6 months before diagnosis (p=0.001) was significantly associated with poor overall survival (Tab. 6).

Table 1. Characteristics of patients*

Characteristics	Induction (n=32)	Concurrent (n=41)	p value
Age (years)			0.107
Median	58	61	
Range	42–70	32–74	
Gender			0.456
Male	28 (88)	38 (93)	
Female	4 (12)	3 (7)	
Performance status			0.015
0	3 (9)	1 (2)	
1	28 (88)	29 (71)	
2	1 (3)	11 (27)	
Weight loss			0.445
No	14 (44)	14 (34)	
0 – 5%	5 (16)	4 (10)	
5 – 10%	10 (31)	14 (34)	
>10%	3 (9)	6 (15)	
Unknown		3 (7)	
Histologic type			0.363
Squamous cell	18 (56)	28 (68)	
Adenocarcinoma	9 (28)	6 (15)	
Non-small cell	5 (16)	7 (17)	
Stage			0.060
IIIA	3 (9)	11 (27)	
IIIB	29 (91)	30 (73)	

*percentages in parentheses

Table 2. Toxicity of induction chemotherapy (n=32)*

Grade	1	2	3	4
Leukopenia	5 (16)	7 (22)	5 (16)	
Neutropenia		3 (9)	3 (9)	5 (16)
Anemia	13 (41)			
Thrombocytopenia	2 (6)			
Nause/vomiting	10 (31)	9 (28)	1 (3)	
Oral mucositis	2 (6)			
Diarrhea	1 (3)			
Liver	5 (16)	1 (3)	1 (3)	
Fever of unknown origin		2 (6)		
Pneumonia (infectious)	1 (3)			

*percentages in parentheses

Table 3. Toxicity of concurrent chemoradiotherapy by treatment group[*,**,***]

	Induction (n=29)[****]				Concurrent (n=41)			
Grade	1	2	3	4	1	2	3	4
Leukopenia	4 (14)	4 (14)	1 (3)		7 (17)	7 (17)	5 (12)	2 (5)
Neutropenia	1 (4)	2 (7)			6 (15)	6 (15)	3 (7)	1 (2)
Anemia	6 (21)	5 (17)	1 (3)		11 (27)	7 (17)	4 (10)	1 (2)
Thrombocytopenia	2 (7)	1 (3)			5 (12)	1 (2)	3 (7)	1 (2)
Nause/vomiting	9 (31)	6 (21)			9 (22)	9 (22)	2 (5)	
Oral mucositis	1 (3)							
Diarrhea	1 (3)				3 (7)			
Constipation			1(3)					
Liver				1(3)	2 (5)		1(2)	
Kidney	2 (7)				6 (15)			
Fever of unknown origin	1 (3)	3 (10)			1 (2)	8(20)		
Radiation pneumonitis	11 (38)	10 (35)			20 (49)	9 (22)		
Radiation esophagitis	18 (62)	3 (10)	1 (3)		17 (42)	9 (22)		
Radiation dermatitis	4 (14)				8 (20)		1(2)	

[*]percentages in parentheses, [**]none of differences was statistically significant, [***]there was 1 patient with grade V toxicity: tracheoesophageal fistula in induction group, [****]excluding 3 patients with palliative radiotherapy or without radiotherapy

Table 4. Response to chemoradiotherapy[*]

Response	Induction (n=29)[**]	Concurrent (n=41)	p value
Complete response	1(3)	2 (5)	0.560
Partial response	11 (38)	20 (49)	
Stable disease	7 (24)	11 (27)	
Progression	10 (35)	8 (20)	

[*]percentages in parentheses, [**]excluding 3 patients with palliative radiotherapy or without radiotherapy

Table 5. Pattern of first treatment failure[*]

Site	Induction (n=32)	Concurrent (n=41)	p value
Locoregional	18 (56)	18 (44)	0.214
Distant	5 (16)	9 (22)	
Both	5 (16)	6 (15)	
Undetermined	2 (6)	8 (20)	
No progression	2 (6)		

[*]percentages in parentheses

Discussion

In our institution, locally advanced unresectable IIIA/IIIB NSCLC patients had been treated with radiotherapy and concurrent daily low dose cisplatin since March 1995 based on the encouraging results of EORTC trial [4]. Since January 1997, we have attempted to combine sequential and concurrent CRT because both treatments are known to have beneficial effect on systemic metastasis and primary tumor, respectively [2]. Therefore, unresectable NSCLC patients with good PS were primarily considered as candidates for induction chemotherapy followed by CRT.

Unlike our expectation, combined induction chemotherapy and concurrent CRT did not improve treatment results in terms of response rate, PFS and OS compared to concurrent CRT alone with a tendency of inferior PFS and OS in induction group. Furthermore, incidence of distant metastasis was not decreased with additional induction chemotherapy. These results are somewhat disappointing considering the fact that combined treatment group had a higher proportion of patients with good PS than CRT alone group.

While few randomized trials have demonstrated superior treatment outcome of concurrent CRT over induction chemotherapy followed by radiotherapy, induction chemotherapy followed by concurrent CRT was compared with concurrent CRT alone in two randomized trials without significant advantage of adding induction chemotherapy to concurrent CRT [15–20]. Only one phase II trial investigated induction chemotherapy followed by CRT with sensitizing single agent cisplatin. ARDIZZONI et al [9] reported 56% of response rate and 12.5 months of median survival (2-year survival: 26%) in 32 patients treated with 2 cycles of induction chemotherapy with vinblastine and cisplatin followed by radiotherapy with concurrent daily low-dose cisplatin, which was comparable with the results of induction group in the present study.

One possible explanation for failure of improving survival by adding induction chemotherapy is relatively low response rate (16%) of induction chemotherapy in the present study. However, 2 cycles of vinblastine/cisplatin regimen, which has been frequently used in induction chemotherapy for locally advanced NSCLC, showed similar response rate (13–26%) in other trials [5, 21]. In addition, response after induction chemotherapy could be inaccurate because it was evaluated only by plain chest X-ray in the current study. Recently, combination chemotherapy regimens containing new chemotherapeutic agents such as docetaxel, paclitaxel, and gemcitabine are being used for advanced NSCLC with high response rate [22]. In the current study, relatively small proportion (25%) of patients received induction chemotherapy with new agents containing regimen. Therefore, there is a possibility that the therapeutic efficacy of induction chemotherapy with concurrent CRT could be improved with integration of new chemotherapeutic agents in induction chemotherapy. However, two recent randomized trials with chemotherapy regimens including new agent did not demonstrate the benefit of adding induction chemotherapy to concurrent CRT [20, 23]. A randomized phase II trial compared three arms consisted of induction chemotherapy with pacli-

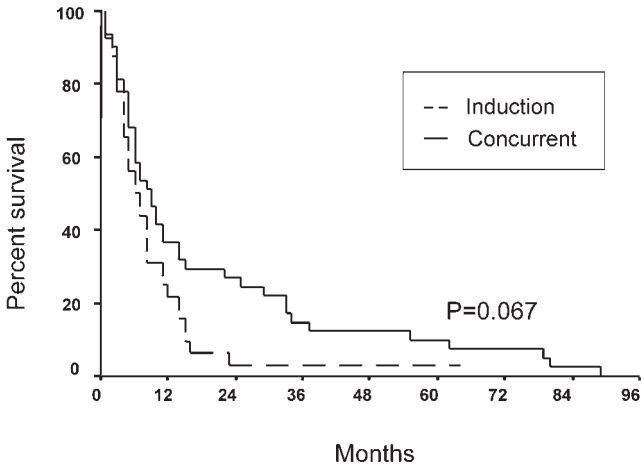

Figure 1. Progression-free survival by treatment groups.

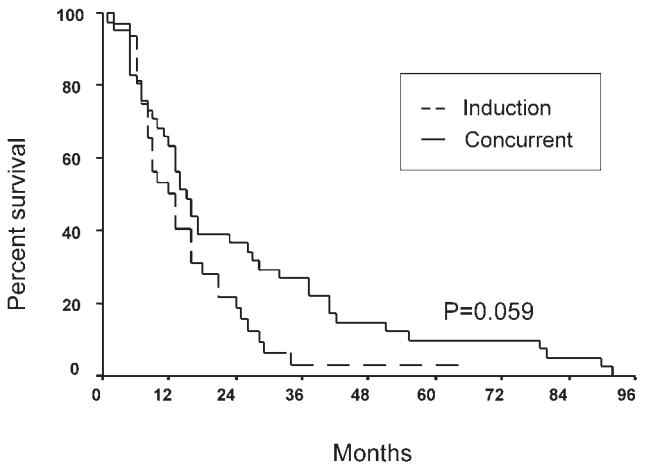

Figure 2. Overall survival by treatment groups.

Table 6. Mutivariate analysis of overall survival

Prognostic factors	Hazard raio	95% CI*	p value
Gender			
Male	1.00		
Female	1.74	0.73 – 4.13	0.208
Age			
≤60	1.00		
>60	0.64	0.37 – 1.10	0.107
Weight loss			
No	1.00		
0 – 5%	0.72	0.30 – 1.71	0.456
5 – 10%	1.56	0.84 – 2.87	0.156
>10%	4.30	1.76 – 10.5	0.001
ECOG PS			
0,1	1.00		
2	0.46	0.20 – 1.04	0.062
Histologic tupe			
Squamous cell	1.00		
Adenocarcinoma	0.97	0.48 – 1.95	0.923
Non-small cell	0.72	0.36 – 1.44	0.357
Stage			
IIIA	1.00		
IIIB	1.61	0.80 – 3.22	0.184
Treatment			
Concurrent	1.00		
Induction	1.31	0.76 – 2.24	0.329

CI* – confidence interval

taxel and carboplatin followed by radiotherapy alone or radiotherapy with weekly paclitaxel and carboplatin, and concurrent radiotherapy with weekly paclitaxel and carboplatin followed by adjuvant chemotherapy with the same agents [23]. In this trial, concurrent CRT followed by adjuvant chemotherapy had the best therapeutic outcome while induction chemotherapy with concurrent CRT showed inferior median survival compared with other two arms [23]. Furthermore, in a phase III trial with 366 patients, the addition of 2 cycles of induction chemotherapy with paclitaxel and carboplatin to concurrent CRT with the same agents failed to improve response rate and survival [20].

In induction group, 4 patients received only radiotherapy without cisplatin due to decreased performance status or refused further CRT after induction chemotherapy. In addition, disease progression was observed in 5 patients (16%) after induction chemotherapy. These findings could be another explanation of inferior treatment results in induction group and suggest that initiation of CRT as early as possible would be important to get the best therapeutic outcome.

Although the present study was not randomized with small sample size, the results rather reflect the effect of CRT for unresectable NSCLC in routine clinical practice. The median survival of 14.5 months and 37% of 2-year survival rate in concurrent CRT group compares favorably with those of EORTC and CALGB trials, considering the fact that this group included significant number of patients with poor prognostic factors including ECOG PS 2 and more than 10% weight loss before diagnosis, who are usually not eligible for clinical trial [4, 5].

Toxicity of CRT was generally mild and acceptable compared with other clinical trials in both groups [4, 15, 18, 19, 23, 24]. In terms of radiation pneumonitis and esophagitis, which have been reported as frequent and potentially serious complications in concurrent CRT, severe (grade 3 or higher) radiation esophagitis was observed in only 1 patient in induction group and all cases of radiation pneumonitis were grade 1 or 2 in both groups [4, 15, 18, 19, 23, 24]. Lethal toxic effect was reported in 1 patient (1.4%), which compares favorably with the rates reported in other trials [3–5, 7, 9, 19, 24, 25]. However, a quarter of patients experienced grade 3/4 neutropenia or leukopenia during induction chemotherapy.

Considering relatively mild toxicity of CRT with low dose cisplatin and a trend toward inferior survival in induction group in the present study, there is a concern that induction chemotherapy might add unnecessary side effects without improving treatment outcome.

Although large scale prospective randomized trials are warranted to prove the best sequencing of CRT, the current retrospective analysis suggests the possibility that induction chemotherapy followed by concurrent CRT does not provide additional benefit compared with concurrent CRT alone.

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